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(54) **PHARMACEUTICAL COMPOSITION CONTAINING A FUSIBLE CARRIER AND METHOD FOR PRODUCING THE SAME**

PHARMAZEUTISCHE ZUSAMMENSETZUNG MIT EINEM SCHMELZBAREN TRAEGERMATERIAL
UND VERFAHREN ZU SEINER HERSTELLUNG

COMPOSITION PHARMACEUTIQUE CONTENANT UN VECTEUR FUSIBLE ET SON PROCEDE
DE FABRICATION

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Description

[0001] The present invention relates generally to a method of manufacturing pharmaceutical dosage forms, for human or veterinary use, preferably sustained release particles, such particles having diameters ranging from 0.1 to 3.0mm. Such particles may contain analgesics, such as morphine, or other active ingredients. The present invention also relates to dosage forms obtained by processing of the aforesaid particles, such as tablets, suppositories or pessaries.

[0002] In our co-pending British Patent Application No. 9404928.5 we describe a process for the manufacture of particles, preferably sustained release particles, which comprises

- (a) mechanically working in a high-shear mixer, a mixture of a particulate drug and a particulate, hydrophobic and/or hydrophilic fusible carrier or diluent having a melting point from 35 to 150°C and optionally a release control component comprising a water-soluble fusible material or a particulate, soluble or insoluble organic or inorganic material, at a speed and energy input which allows the carrier or diluent to melt or soften whereby it forms agglomerates;
- (b) breaking down the agglomerates to give controlled release particles: and optionally
- (c) continuing mechanically working optionally with the addition of a low percentage of the carrier or diluent; and optionally
- (d) repeating steps (c) and possibly (b) one or more times.

[0003] We have now found that satisfactory results may also be obtained if, instead of classifying the agglomerated material in stage b) the material from stage a) is formed into extrudates of predetermined size, and in preferred embodiments, higher yields and/or higher drug loadings, and greater uniformity of size, than in the earlier process first mentioned above still with satisfactory controlled release properties may be achieved.

[0004] The present invention thus includes in one aspect a process for the manufacture of particles, preferably sustained release particles, which comprises:-

- (a) mechanically working in a high-shear mixer, a mixture of a particulate drug and a particulate, hydrophobic and/or hydrophilic fusible carrier or diluent having a melting point from 35 to 150°C and optionally a release control component comprising a water soluble fusible material or a particulate, soluble or insoluble, organic or inorganic material, at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates; and then
- (b) extruding the resulting material.
The extrusion may be carried out so as to form a rod like extrudate which may be cut or moulded to form unit dosage forms e.g. tablets or suppositories, directly.
Preferably the extrusion is through a plurality of orifices and the extrudate is formed into pieces. In more preferred embodiments the extrusion is through a plurality of small orifices e.g. about 0.25mm to 1.5mm e.g. 0.5mm or 1.0mm diameter and the extrudate is formed into short lengths of e.g. 0.5 to 1.5mm e.g. 1.0mm, suitably by cutting.
- (c) continuing mechanically working the pieces formed from the extrudate, optionally with a further addition of a low percentage of the carrier or diluent; and
- (d) optionally repeating step (c) and possibly (b) one or more e.g. up to five times.

[0005] Extrusion and forming into short lengths by cutting may be carried out using e.g. an Alexanderwerk, Caleva or Nica machine.

[0006] Extrusion operations are well known in the formulation field and described, for example in Pharmaceutical Dosage Forms, Volume 2, Ed. Lieberman and Lachman, Marcel Dekker Inc, New York and Basel.

[0007] This process is capable of giving a high yield, generally greater than 85%, and preferably greater than 90% of particles in a desired size range, with a desired in vitro release rate and, uniformity of release rate.

[0008] The resulting particles may be sieved to eliminate any oversized or undersized material then formed into the desired dosage units by, for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by tableting, filling into sachets or moulding into suppositories, pessaries or forming into other suitable dosage forms.

[0009] The drug may be water soluble or water insoluble. Water soluble drugs will usually be used in amounts giving for example a loading of up to about 90% w/w in the resulting particles; water insoluble drugs may be used in higher amounts eg. up to 99% w/w of the resulting particles; Examples of water soluble drugs which can be used in the method of the invention are morphine, hydromorphone, diltiazem, diamorphine and tramadol and pharmaceutically acceptable salts thereof; examples of water insoluble drugs which can be used in the process of the invention are naproxen, ibuprofen, indomethacin and nifedipine.

[0010] In EP-A- 204596 a process is disclosed where a already fused carrier is mixed with a particulate active material not in a high-shear mixer but in a planetary mixer at 50 rpm.

[0011] Among the active ingredient which can be used in the process of the invention are the following;

ANALGESICS and ANTIINFLAMMATORIES

[0012] Dihydrocodeine, , Hydromorphone, Morphine, Diamorphine, Fentanyl, Alfentanil, Sufentanyl, Pentazocine, Buprenorphine, Nefopam, Dextropropoxyphene, Flupirtine, Tramadol, Oxycodone, Metamizol, Propyphenazone, Phenazone, Nifnazone, Paracetamol, Phenylbutazone, Oxyphenbutazone, Mofebutazone, Acetyl salicylic acid, Diflunisal, Flurbiprofen, Ibuprofen, Diclofenac, Ketoprofen, Indomethacin, Naproxen, Meptazinol, Methadone, Pethidine, Hydrocodone, Meloxicam, Fenbufen, Mefenamic acid, Piroxicam, Tenoxicam, Azapropazone, Codeine,

ANTIALLERGICS

[0013] Pheniramine, Dimethindene, Terfenadine, Astemizole, Tritoqualine, Loratadine, Doxylamine, Mequitazine, Dexchlorpheniramine, Triprolidine, Oxatomide,

ANTIHYPERTENSIVE

[0014] Clonidine, Moxonidine, Methyldopa, Doxazosin, Prazosin, Urapidil, Terazosin, Minoxidil, Dihydralazin, Deserpidine, Acebutalol, Alprenolol, Atenolol, Metoprolol, Bupranolol, Penbutolol, Propranolol, Esmolol, Bisoprolol, Ciliprolol, Sotalol, Metipranolol, Nadolol, Oxprenolol, Nifedipine, Nicadipine, Verapamil, Diltiazem, Felodipine, Nimodipine, Flunarizine, Quinapril, Lisinopril, Captopril, Ramipril, Fosinopril, Cilazapril, Enalapril,

ANTIBIOTICS

[0015] Demodocycline, Doxycycline, Lymecycline, Minocycline, Oxytetracycline, Tetracycline, Sulfametopyrazine, Ofloxacin, Ciproflaxacin, Aerosoxacin, Amoxycillin, Ampicillin, Becampicillin, Piperacillin, Pivampicillin, Cloxacillin, Penicillin V, Flucloxacillin, Erythromycin, Metronidazole, Clindamycin, Trimethoprim, Neomycin, Cefaclor, Cefadroxil, Cefixime, Cefpodoxime, Cefuroxime, Cephalexin, Cefradine.

BRONCHODILATOR/ANTI-ASTHMATIC

[0016] Pirbuterol, Orciprenaline, Terbutaline, Fenoterol, Clenbuterol, Salbutamol, Procaterol, Theophylline, Cholintheophyllinate, Theophylline-ethylenediamine, Ketofen,

ANTIARRHYTHMICS

[0017] Viquidil, Procainamide, Mexiletine, Tocainide, Propafenone, Ipratropium,

CENTRALLY ACTING SUBSTANCES

[0018] Amantadine, Levodopa, Biperiden, Benzotropine, Bromocriptine, Procydidine, Moclobemide, Tranclypromide, Clomipramine, Maprotiline, Doxepin, Opipramol, Amitriptyline, Desipramine, Imipramine, Fluoxamin, Fluoxetin, Paroxetine, Trazodone, Viloxazine, Fluphenazine, Perphenazine, Promethazine, Thioridazine, Triflupromazine, Prothipendyl, Tiotixene, Chlorprothixene, Haloperidol, Pipamperone, Pimozide, Sulpiride, Fenethylamine, Methylphenidate, Trifluoperazine, Thioridazine, Oxazepam, Lorazepam, Bromazepam, Alprazolam, Diazepam, Clobazam, Buspirone, Piracetam,

CYTOSTATICS AND METASTASIS INHIBITORS

[0019] Meifalan, Cyclophosphamide, Trofosfamide, Chlorambucil, Lomustine, Busulfan, Prednimustine, Fluorour-

acil, Methotrexate, Mercaptopurine, Thioguanin, Hydroxycarbamide, Altretamine, Procarbazine,

ANTI-MIGRAINE

5 [0020] Lisuride, Methysergide, Dihydroergotamine, Ergotamine, Pizotifen,

GASTROINTESTINAL

10 [0021] Cimetidine, Famotidine, Ranitidine, Roxatidine, Pirenzepine, Omeprazole, Misoprostal, Proglime, Cisapride, Bromopride, Metoclopramide,

ORAL ANTIDIABETICS

15 [0022] Tobutamide, Glibenclamide, Glipizide, Gliquidone, Gliboruride, Tolazamide, Acarbose and the pharmaceutically active salts or esters of the above and combination of two or more of the above or salts or esters thereof.

[0023] The hydrolysis of drugs constitutes the most frequent, and perhaps therefore the most important, route of drug decomposition. Analysis of a collection of stability data in Connors KA, Amidon GL, Stella VI, Chemical stability of pharmaceuticals. A handbook for pharmacists, 2nd ed. New York: John Wiley & Sons, 1986, a standard text, shows that over 70% of the drugs studied undergo hydrolytic degradation reactions. Of these, 61.4% can be classed as reactions of carboxylic acid derivatives (esters, amides, thiol esters, lactams, imides), 20% of carbonyl derivatives (imines, oximes), 14.3% of nucleophilic displacements, and 4.3% of phosphoric acid derivatives. Cephalosporins, penicillins and barbituates are particularly susceptible drug classes.

[0024] The process of the invention may advantageously be used for preparing dosage forms containing active substances as mentioned above which are unstable in the presence of water, e.g. diamorphine. Thus stable formulations of such drugs having normal or controlled release characteristics can be obtained in accordance with the invention.

[0025] In a preferred method according to the invention morphine sulphate, or other water soluble drug, e.g. tramadol, is used in an amount which results in particles containing e.g. between <1% and 90%, especially between about 45% and about 85% e.g. 75 w/w active ingredient for a high dose product and e.g. <1 and 45% for a low dose product.

20 [0026] In the method of the invention preferably all the drug is added in step (a) together with a major portion of the hydrophobic or hydrophilic fusible carrier or diluent used. Preferably the amount of fusible carrier or diluent added in step (a) is between e.g. 10% and <99% w/w of the total amount of ingredients added in the entire manufacturing operation.

[0027] In step (c) the amount of optional additional fusible carrier or diluent added is preferably between 5% and 75% w/w of the total amount of ingredients added. The additional material may be added stepwise.

35 [0028] Stage (a) of the process may be carried out in conventional high-shear mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature above 40°C is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1-3mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40°C have structural integrity and resistance to crushing between the fingers. At this stage the size/agglomerates are of an irregular shape and appearance. The resulting mass is then extruded as described above.

40 [0029] In one preferred form of the process of the invention processing of the extruded materials is continued, until the hydrophobic and/or hydrophilic fusible carrier or diluent materials used begin to soften or melt and additional hydrophobic and/or hydrophilic fusible carrier or diluent material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

[0030] In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

[0031] Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

50 [0032] After the particles have been formed they are sieved to remove any over or undersized material and then cooled or allowed to cool.

[0033] The resulting particles may be used to prepare dosage units e.g. tablets or capsules in manners known *per se*.

[0034] We have found that by suitable selection of the materials used in forming the particles and in the tableting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the active ingredients from the compressed tablets.

55 [0035] Suitable substances for use as hydrophobic carrier or diluent materials are natural or synthetic waxes or oils, for example hydrogenated vegetable oil, hydrogenated castor oil, beeswax, camuba wax, microcrystalline wax and glycerol monostearate, and suitably have melting points of from 35 to 150°C, preferably 45 to 90°C.

[0036] Suitable substances for use as hydrophilic carrier or diluent are Polyethylene glycols (PEGs) of various molecular weights e.g. 1,000 to 20,000, preferably 4,000 to 10,000.

[0037] The optionally added release control component when a water soluble, fusible material may be a PEG of appropriate molecular weight; suitable particulate inorganic and organic materials are dicalcium phosphate, colloidal anhydrous silica, calcium sulphate, talc, lactose, poloxamers, microcrystalline cellulose, starch, hydroxy propylcellulose, hydroxy propylmethyl cellulose.

[0038] In this process of the invention the temperature of the mixing bowl throughout the mechanical working is chosen so as to avoid excessive adhesion, suitably to minimise adhesion of the material to the walls of the bowl. To minimise adhesion we have generally found that the temperature should be neither too high nor too low with respect to the melting temperature of the material and it can be readily optimised to avoid the problems mentioned above. For example in the processes described below in the Examples a bowl temperature of approximately 50 - 60°C has been found to be satisfactory and avoids adhesion to the bowl. It is not possible to generalise as to the appropriate temperature or period for the mechanical working for any particular mixture to be processed. However, in practice, it is a matter of simple experimentation and observations to establish a suitable temperature and processing time for a particular mixture under consideration.

[0039] To produce tablets in accordance with the invention, particles produced as described above may be mixed or blended with the desired excipient(s), if any, using conventional procedures e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tableting procedure using a suitably sized tableting tooling. Tablets can be produced using conventional tableting machines, and in the embodiments described below were produced on standards single punch F3 Manesty machine or Killan RLE15 rotary tablet machine.

[0040] Generally speaking we find that even with highly water soluble active agents such as salts of morphine or tramadol, tablets formed by compression according to standard methods give very low *in vitro* release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the *in vitro* release profile can be adjusted in a number of ways. For instance in the case of water soluble drugs a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tableting formulation will also be associated with a higher release rate of the active ingredient. Thus, by controlling the relative amounts of these ingredients it is possible to adjust the release profile of the active ingredient, whether this be water soluble or water insoluble.

[0041] In order that the invention may be well understood the following examples are given by way of illustration only.

EXAMPLE

[0042] 700g of finely powdered morphine sulphate and 220g of finely powdered hydrogenated vegetable oil were placed in the bowl of a 10 litre capacity Collette Vactron Mixer (or equivalent) equipped with variable speed mixing and granulating blades. The ingredients were mixed at about 425 rpm with the jacket temperature at 55°C to 65°C, until the contents of the bowl are agglomerated.

The mass is extruded through 1 mm holes of an Alexanderwerk extruder equipped with a cutting blade located so as to cut the extrudate into approximately 1.0mm length pieces.

[0043] The short lengths of extrudate are collected and returned to the warm bowl of the mixer and operation of the mixture is recommenced. After the extrudates become generally rounded, a further 80 gm of finely divided hydrogenated vegetable oil is added to the bowl and mixing is continued for 3 minutes when the extrudates are generally spherical.

[0044] The spherical particles are removed from the bowl, allowed to cool and are then sieved to isolate the sieve fraction 0.5 to 2.0mm.

[0045] The release rates of the sieved particles are then assessed by modified Ph. Eur. Basket method at 100 rpm in 900 ml aqueous buffer (ph 6.5) containing 0.05% w/w polysorbate 80 at 37°C and the results are given below:-

TABLE

HOURS AFTER START OF TEST	% OF MORPHINE SULPHATE RELEASED
1	6
2	11
4	21
8	37
12	48
16	57

TABLE (continued)

HOURS AFTER START OF TEST	% OF MORPHINE SULPHATE RELEASED
24	67
30	72

Claims

1. A process for the manufacture of sustained release particles which comprises
 - (a) mechanically working in a high-shear mixer, a mixture of a particulate drug and a particulate, hydrophobic and/or hydrophilic fusible carrier or diluent having a melting point from 35 to 150°C and optionally a release control component comprising a water-soluble fusible material or a particulate, soluble or insoluble organic or inorganic material, at a speed and energy input which allows the carrier or diluent to melt or soften whereby it forms agglomerates; and
 - (b) extruding the resulting material, through a plurality of orifices, forming the extrudate into pieces,
 - (c) continuing mechanically working the pieces of extrudate optionally with the addition of a low percentage of the carrier or diluent; and optionally
 - (d) repeating steps (c) and possibly (b) one or more times
2. A process according to any one of claim 1, wherein during the mechanical working, heat is supplied thereto by microwave radiation.
3. A process according to claim 2, wherein only part of the heating is supplied by microwave radiation.
4. A process according to any one of claims 1 to 2, wherein the drug is morphine tramadol, hydromorphone, oxycodone, diamorphine or a pharmaceutically acceptable salt of any one of these.
5. A process according to any one of claims 1 to 4, wherein the hydrophobic fusible carriers(s) or diluent(s) is a wax, e.g. chosen from hydrogenated vegetable oil, hydrogenated castor oil, Beeswax, Carnauba wax, microcrystalline wax and glycerol monostearate.
6. A process according to any one of claims 1 to 5, wherein the hydrophilic fusible material optionally included in the mixture in step (a) is PEG having a molecular weight of from 1,000 to 20,000, or a poloxamer.
7. A process according to any one of claims 1 to 6 wherein the fusible carrier or diluent is added stepwise during mechanical working during step (c).

Patentansprüche

1. Verfahren für die Herstellung von Teilchen mit Langzeitwirkung, welches aufweist:
 - (a) mechanisches Bearbeiten in einem Hoch-Schermischer einer Mischung von einem aus Teilchen bestehendem Arzneimittel und einem aus Teilchen bestehendem hydrophoben und/oder hydrophilen schmelzbaren Träger oder Verdünnungsmittel mit einem Schmelzpunkt von 35°C bis 150°C und wahlfrei einer Freigabekontrollkomponente, aufweisend ein wasserlösliches schmelzbares Material oder ein aus Teilchen bestehendes lösliches oder unlösliches organisches oder anorganisches Material mit einer Geschwindigkeit und Energieeigabe, welches es dem Träger oder Verdünnungsmittel erlaubt, zu schmelzen oder zu erweichen, wodurch es Agglomerate bildet; und
 - (b) Extrudieren des sich ergebenden Materials durch eine Vielzahl von Öffnungen, wobei das Extrudat in Stücke gebildet wird,

(c) Fortsetzen des mechanischen Bearbeitens der Extrudatstücke wahlfrei mit der Zugabe eines geringen Prozentsatzes des Trägers oder Verdünnungsmittels; und wahlfrei

(d) Wiederholen von Stufen (c) und möglicherweise (b) ein oder mehrere Male.

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2. Verfahren nach Anspruch 1, wobei während des mechanischen Bearbeitens Wärme mittels Mikrowellenstrahlung darauf geliefert wird.

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3. Verfahren nach Anspruch 2, wobei nur Teil des Erhitzens durch Mikrowellenstrahlung geliefert wird.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei das Arzneimittel Morphin, Tramadol, Hydromorphon, Oxycodon, Diamorphen oder ein pharmazeutisch verträgliches Salz von einem dieser ist.

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5. Verfahren nach einem der Ansprüche 1 bis 4, wobei der (die) hydrophobe(n) schmelzbare(n) Träger oder Verdünnungsmittel ein Wachs ist, beispielsweise ausgewählt aus hydriertem Pflanzenöl, hydriertem Castoröl, Bienenwachs, Carnaubawachs, mikrokristallinem Wachs und Glycerol-monostearat.

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6. Verfahren nach einem der Ansprüche 1 bis 5, wobei das hydrophile schmelzbare Material, welches wahlfrei in der Mischung in Stufe (a) eingeschlossen ist, PEG mit einem Molekulargewicht von 1 000 bis 20 000 oder ein Poloxamer ist.

7. Verfahren nach einem der Ansprüche 1 bis 6, wobei der schmelzbare Träger oder Verdünnungsmittel stufenweise während des mechanischen Bearbeitens während Stufe (c) hinzugefügt wird.

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Revendications

1. Procédé pour la fabrication de particules à libération prolongée, qui comprend:

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(a) le travail mécanique, dans un mélangeur à haut cisaillement, d'un mélange de médicament particulaire et d'un véhicule ou diluant particulaire fusible, hydrophobe et/ou hydrophile, ayant un point de fusion de 35 à 150°C et, facultativement, d'un constituant à libération régulée comprenant une matière hydrosoluble fusible ou une matière organique ou inorganique particulaire, soluble ou insoluble, à une vitesse et une entrée d'énergie qui permettent au véhicule ou diluant de fondre ou ramollir de sorte qu'il forme des agglomérats; et

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(b) l'extrusion de la matière résultante à travers plusieurs orifices de manière à façonner le produit d'extrusion en pièces,

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(c) la poursuite du travail mécanique des pièces extrudées, en ajoutant facultativement un faible pourcentage du véhicule ou diluant; et, facultativement

(d) la répétition des étapes (c) et éventuellement (b) une ou plusieurs fois.

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2. Procédé selon la revendication 1, dans lequel, pendant le travail mécanique, de la chaleur est fournie par radiation micro-onde.

3. Procédé selon la revendication 2, dans lequel seule une partie du chauffage est fournie par radiation micro-onde.

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4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel le médicament est la morphine, le tramadol, l'hydromorphone, l'oxycodone, la diamorphine ou un sel pharmaceutiquement acceptable de l'un quelconque de ceux-ci.

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5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le(s) véhicule(s) ou diluant(s) fusible(s) hydrophobe(s) est (sont) une cire, choisie par exemple parmi une huile végétale hydrogénée, l'huile de ricin hydrogénée, la cire d'abeilles, la cire de carnauba, une cire microcristalline et le monostéarate de glycérol.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel la matière hydrophile fusible facultativement incluse dans le mélange de l'étape (a) est un PEG ayant un poids moléculaire de 1 000 à 20 000 ou un poloxamère.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel le véhicule ou diluant fusible est ajouté par étapes pendant le travail mécanique de l'étape (c).

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